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EXAMINER	
REDDIG, PETER J	

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1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/531,415	BERDEL ET AL.	
	Examiner	Art Unit	
	PETER J. REDDIG	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-39,41-53,58-64 and 73-77* is/are pending in the application.

4a) Of the above claim(s) *61-64 and 73-76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-39,41-53,58-60 and 77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/12/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Election filed May 8, 2008 in response to the Office Action of November 1, 2007 is acknowledged and has been entered.

Applicant's election with traverse of Group I, claims 37-39, 41-53, and claims 58-60 and the species A-1 (peptide/oligopeptide/protein/fusion protein) and species B-1 (a DNA binding domain is acknowledged.

Applicants argue that the Office has not proven that the search and examination of the entire application would impose an undue burden. Applicants submit that the complete examination would be handled most expeditiously by treating all of the pending claims as a single entity. As MPEP §803 directs, "[i]f the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions." Applicants respectfully submit that the Examiner has not shown that a search and examination of the entire application would cause a serious burden. Rather, a serious burden would arise if the application were restricted.

Applicants' arguments have been considered, but have not been found persuasive because burden of search is not a requirement for a finding of lack of unity under PCT Rule 13.1 and 13.2.

Applicants argue that the restriction requirement is inappropriate. For example, Applicants contend that Groups I and II should be examined simultaneously because they are related as a nucleic acid encoding the protein of claim 53. Applicants argue that the Examiner alleges that the inventions of Groups I-IV have no special technical feature that defined the contribution over the prior art of Vigneri and Wang (Nature Medicine, Feb. 7, 2001, pp. 228-

234). Office Action at page 3. Thus, the Examiner argues that method of the present invention cannot be considered a special technical feature, as lack of unity rules hold that a feature known to a person of ordinary skill in the art makes no advance over the prior art. Applicants argue that the Examiner has mistaken the claimed invention and the technical feature described in Vigneri and Wang to be the same.

Applicants' arguments have been considered, but have not been found persuasive because Applicants have not pointed out the differences between Vigneri and Wang and BCR-Abl reads on the compound of claim 37, see section 10 below. Therefore, the technical feature linking the inventions of Groups 1-4 does not constitute a special technical feature as defined by PCT Rule 13.2 as it does not define a contribution over the prior art. Furthermore, the claims of Group 2, claims 54-57, are no longer pending, thus arguments with regard to Group 2 are moot. Additionally the inventions of groups 1-4 are drawn to multiple products as well as multiple methods of using those products. Allowed combinations do not include multiple products, and multiple methods of using said products, as claimed in the instant application. Hence, only one product and one process of use of said product relate to a single general inventive concept, see 37 C.F.R. 1.475and 1.476. However, upon review and reconsideration the species of Group 1B will be rejoined. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Claims 37-39, 41-53, 58-64 and 73-77 are pending. Claims 61-64 and 73-76 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 37-39, 41-53, 58-60 and 77 are currently under consideration as drawn to the elected species of compound A-1 (peptide/oligopeptide/protein/fusion protein).

Priority

2. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Germany on 10/18/2002. It is noted, however, that applicant has not filed a certified copy of the 102 48 751.0 application as required by 35 U.S.C. 119(b).

Thus, it is noted that, in the absence of the German patent application, the examiner has established a priority date for the instant application, 10/531,415 of October 17, 2003 because the priority of the instantly claimed invention is based on the German patent application No. 102 48 751.0. If applicant disagrees with any rejection set forth in this action based on examiner's establishment of a priority date, October 17, 2003, for the instantly claimed application serial number 10/531,415, applicant is invited to submit a certified copy with a translation of the priority document and to point to, page and line where support can be found establishing an earlier priority date. If applicant chooses to file a translation, then the translation must be filed together with a statement that the translation of the certified copy is accurate, see MPEP 201.15.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claims 37-39, 41-53, and 77 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 37-39, 41-53, and 77, as written, do not sufficiently distinguish over the claimed polypeptide compounds as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v.*

Chakrabarty, 447 U.S. 303, 206 USPQ 193 (1980). In order to obviate the instant rejection, the Examiner suggests that the claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated" or "purified" provided the support for such an amendment can be identified in the specification as originally filed. See MPEP 2105.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 42 and 43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 42 and 43 are drawn to the compound of claim 37 wherein the first binding domain has a binding affinity of 10^{-5} to 10^{-12} or a binding affinity of 10^{-7} to 10^{-9}. However, the claims have no limitation as to the units of the claimed binding affinities or to what binding the binding affinities refer. Thus, in the absence of units for the affinity or what binding interaction refers to, it can not be determined what the scope of the binding affinity is.

Section 2171 of the M.P.E.P. states

> *There are two separate requirements set forth in this paragraph:*
> *(A) the claims must set forth the subject matter that applicants regard as their invention; and*
> *(B) the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant.*
>
> *The first requirement is a subjective one because it is dependent on what the applicants for a patent regard as their invention. The second requirement is an objective one because it is not dependent on the views of applicant or any particular individual, but is evaluated in the context of whether the claim is definite — i.e., whether the scope of the claim is clear to a hypothetical person possessing the ordinary level of skill in the pertinent art.*

In the instant case of the claimed binding affinities, one of skill in the art could find representative examples in the art which have been defined in such terms, however, it is unclear at what point one of skill in the art would be infringing on the claims without limitations as to the metes and bounds of the binding affinities and the amount of deviation acceptable

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 58-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound comprising a binding domain for a tumor-specific molecule and a DNA-binding domain, wherein said compound is a peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor- specific molecule, *does not* reasonably provide enablement for **a medicament** comprising a compound comprising a binding domain for a tumor-specific molecule and a DNA-binding domain, wherein said compound is a peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor-specific molecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations."

(Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a medicament comprising a compound comprising a binding domain for a tumor-specific molecule and a DNA-binding domain, wherein said compound is a peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor-specific molecule. The specification teaches that the present invention further relates to the use of the compound according to the invention for the preparation of a medicament for the treatment of tumors, leukemias, especially acute myeloid leukemia. The treatment of an acute myeloid leukemia caused by a t(8; 21) translocation is particularly preferred. Thus, a reasonable interpretation of the claims 58-60 is that the medicament is for the treatment of cancers.

The specification teaches that a recombinant fusion protein was constructed from the AML1 binding domain of the myeloid like ELF factor (MEF), the DNA binding domain of c-myb and the green fluorescent protein (GFP) and was called GFP-M&M, see p. 20-21. The specification teaches that GFP-M&M binds to MYB DNA binding sites, binds AML1-ETO to c-kit promoter elements, inhibits myb dependent promoter activity in the presence of AML1-ETO, inhibits colony formation of the hematopoietic 32D cell line expressing AML1-ETO, induces apoptosis in the AML1-ETO hematopoietic 32D cells, and did not repress MYB dependent promoters in the absence of AML1-ETO, See pages 21-25 and the figures.

One cannot extrapolate the teachings of the specification to enable the scope of the claims because the development of cancer therapeutics is highly unpredictable and the in vitro cell culture data cannot be predictably extrapolated to the in vivo situation as it is well known in the art that cell culture studies are artifactual and not predictably applicable to the in vivo situation.

In particular, as drawn to the development of cancer therapeutics, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models that only 29 have actually been shown to be useful for chemotherapy (p. 1041, see 1st and 2nd para.). Furthermore, Kaiser (Science, 2006, 313: 1370) teaches that 90% of tumor drugs fail in patients, see 3rd col., 2nd to last para. Because of the known unpredictability of the art, in the absence of experimental evidence in an appropriate *in vivo* model, with data commensurate in scope with the invention claimed no one skilled in the art would accept the assertion that the claimed compound would be an effective medicament for treatment of cancer based only on the *in vitro* cell culture data because the characteristics of cultured cell lines generally differ significantly from the characteristics of primary tumor cells. As discussed in Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p. 4), it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without

this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, a petri dish cancer is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer further teaches that when a normal or malignant cell adapts to immortal life in culture, it takes an evolutionary-type step that enables the new line to thrive in its artificial environment and thus transforms a cell from one that is stable and differentiated to one that is not. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Further, the art recognizes the problem of molecular artifacts associated with cell culture. For example, Drexler et al. (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded. Drexler et al. further teach that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). More recently, Zips et al. (In vivo, 2005, 19:1-7) specifically teaches that despite their importance for drug testing, *in vitro* methods are beset by pitfalls and inherent limitations (p. 3, col. 1). In particular the authors state that "It is obvious that cells in culture represent an artificial and simplified

system. Unlike the situation *in vitro,* a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularisation, perfusion and thereby, drug access to the tumor cells are not evenly distributed and in this fact consists an important source of heterogeneity in tumor response to drugs that does not exist *in vitro.* Therefore, prediction of drug effects in cancer patients based solely on *in vitro* data is not reliable and further evaluations in animal tumor systems is essential" (p. 3, col. 2). Additionally Clark et al. (US Pat. App. Pub. 2006/0019256, January 2006) teach that "[a]lthough cell lines have led to remarkable advances in our understanding of the molecular and biochemical changes in cancer cells, their use in the identification of effective cancer therapies is somewhat limited. Cell lines are imperfect predictors of drug efficacy in de novo tumors. Several factors likely account for this deficiency. Cancer cell lines are selected from a sub-population of cancer cells that are specifically adapted to growth in tissue culture and the biological and functional properties of these cell lines can change dramatically. Furthermore, cancer cells from only a minority of breast cancer tumors establish cell lines or xenograft tumors. The phenotypic and functional characteristics of these cell lines can change drastically relative to their properties in vivo. For example, the marker expression of both normal hematopoietic and leukemic tissue culture cells can change rapidly in tissue culture and often does not reflect that of the original stem cells from which they were derived. Even when conditions are devised to permit the proliferation of normal stem cells in culture, the conditions often promote self-renewal or differentiation in a way that prevents the stem cells in culture from recapitulating the hierarchy of cell populations that exist in vivo. Taken together, these observations suggest that the biological properties of cell lines can differ

markedly from the cancer cells from which they were derived. This likely explains at least in part why the cell lines often are poor predictors of a drug's efficacy in the clinic," see para. 0109. Thus, based on the cell culture data presented in the specification, in the absence of data in an appropriate *in vivo* model, no one of skill in the art would believe it more likely than not that the claimed invention would function as claimed and contemplated, as a medicament for cancer treatment, based only on the cell culture data provided.

In addition, the medicament comprising the claimed compound must accomplish several tasks to be effective. It must be delivered into the circulation that supplies the cancer and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. Also, the target cell must not have an alternate means of survival despite action at the proper site for the medicament. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The medicament may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half-life of the medicament. In addition, the medicament may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where it has no effect, circulation into the target area may be insufficient to carry the medicament and a large enough local concentration may not be established. Thus in absence of appropriate evidence in an in vivo model that the claimed medicament can effectively be delivered in vivo to the appropriate site, given the unpredictability of such a delivery, one of skill in the art would not predictably expect that the medicament would be effective for the treatment of cancer or any other disease. Furthermore, it would not be expected that the

exemplified compound of GFP-M&M/SEQ ID NO: 1, if it were to be effectively delivered to cancer cells, would be effective for treatment of any disease other than cancers expressing the AML1-ETO protein as GFP-M&M/SEQ ID NO: 1 appears to be ineffective in affecting cell growth or apoptosis in the absence of AML1-ETO, see Examples 5 & 6.

Applicant is reminded that MPEP 2164.03 teaches "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 428 F.2d 833, 166 USPQ 18, 24 (CCPA 1970) the amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly state in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling. Given only lack of guidance in the specification, no one skilled in the art would accept the assertion that the claimed invention would function as contemplated or as claimed based only on the information in the specification and that known in the art at the time the invention was made.

The specification provides insufficient guidance with regard to these issues and provides insufficient working examples which would provide guidance to one skilled in the art and insufficient evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed with a reasonable expectation of success.

For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

6. Claims 37-39, 41-53, and 77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound comprising a first binding domain for a tumor-specific molecule and a second binding domain to effect dyslocalization, wherein said compound is a peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor- specific molecule, *does not* reasonably provide enablement for a compound comprising a first binding domain for a tumor-specific molecule and a second binding domain to effect dyslocalization, wherein said compound is a peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor- specific molecule, **wherein the dyslocalization inhibits the growth of tumor cells or induces apoptosis of tumor cells or wherein the dyslocalization binds the tumor-specific molecule to a nucleic acid sequence which regulates the transcription of a gene, thereby activating or inhibiting the transcription of the gene**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the

amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to and encompass a compound comprising a first binding domain for a tumor-specific molecule and a second binding domain to effect dyslocalization, wherein said compound is a peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor- specific molecule, wherein the dyslocalization inhibits the growth of tumor cells or induces apoptosis of tumor cells or wherein the dyslocalization binds the tumor-specific molecule to a nucleic acid sequence which regulates the transcription of a gene, thereby activating or inhibiting the transcription of the gene.

The specification teaches as set forth above.

One cannot extrapolate the teachings of the specification to enable the scope of the claims because it would not predictably be expected that dyslocalization of the broadly claimed tumor specific molecules will inhibit tumor cell growth, induce apoptosis of tumor cells or activate or inhibit any gene because not all tumor specific molecules are directly involved in these processes, these effects are cell type dependent, and dyslocalization of the tumor specific molecule may have the opposite effect. In particular the effect of GFP-M&M appears to be dependent on cells expressing AML1-ETO, see Examples 5 -7. Thus it would not be expected that GFP-M&M would predictably affect these process in tumor cells not expressing AML1-ETO. Furthermore, WO 01/73433 A2 (Minucci et al. October 4, 2001) teaches a fusion protein comprising the coiled coil (CC) region of the transcription factor PML-fused to the full length p53 tumor suppressor protein, see page 61. WO 01/73433 teaches that the CC-p53 protein binds

to p53 through the p53 tetramerization domain and PML CC domain and prevents p53 from entering the nucleus; see pages 61-63 and Fig. 11. WO 01/73433 A2 teaches that CC-p53 inhibits the growth suppressive effect of p53, see p.63 and Fig. 11, thus it does not inhibit the growth of cells. Similarly dyslocalization of other tumor suppressor proteins would not expected to have inhibitory effects on tumor cell growth or induce apoptosis. Additionally, the dyslocalization of tumor markers like CA125 (see Lloyd et al. (Int. J. Cancer 1997 71:842-850)) whose function is not well defined and not associated with affecting cell growth, apoptosis, or gene transcription would not predictably be expected to affect these processes. Given the above, give the breadth of the claims, and given the limited examples provided in the specification, one of skill in the art would not predictably be able to make and use a compound as broadly claimed without undue experimentation.

The specification provides insufficient guidance with regard to these issues and provides insufficient working examples which would provide guidance to one skilled in the art and insufficient evidence has been provided which would allow one of skill in the art to predict that the invention will function as contemplated or claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

7. Claims 37-51, 58-60 and 77 are rejected as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a compound comprising a first binding domain for a tumor-specific molecule and a second binding domain to effect dyslocalization, wherein said compound is a peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor- specific molecule or a compound comprising a binding domain for a tumor-specific molecule and a DNA-binding domain, wherein said compound is a peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor- specific molecule. The claims lack any limitation on said compounds and thus are drawn to a genus of compounds comprising a first binding domain for a tumor-specific molecule and a second binding domain to effect dyslocalization, wherein said compound is a peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor- specific molecule or compounds comprising a binding domain for a tumor-specific molecule and a DNA-binding domain, wherein said compound is a peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor- specific molecule. When given the broadest reasonable interpretation, the terms compound comprising a first binding domain for a tumor-specific molecule and a second binding domain to effect dyslocalization, wherein said compound is a peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor-specific molecule or a compound comprising a binding domain for a tumor-specific molecule and a DNA-binding domain, wherein said compound is a peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor- specific molecule encompasses a wide genus of compounds that is highly variant which vary significantly both in structure and function from each other. The description of GFP-M&M/SEQ ID NO: 1 as a compound comprising a first binding domain for a tumor-specific molecule and a second binding domain to

effect dyslocalization, wherein said compound is a peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor- specific molecule or a compound comprising a binding domain for a tumor-specific molecule and a DNA-binding domain, wherein said compound is a peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor- specific molecule fails to adequately describe the genus of compounds because said genus tolerates members which differ significantly in both structure and function from GFP-M&M/SEQ ID NO: 1. One of skill in the art can reasonably conclude that applicant was not in possession of a genus of a compound comprising a first binding domain for a tumor-specific molecule and a second binding domain to effect dyslocalization, wherein said compound is a peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor- specific molecule or a compound comprising a binding domain for a tumor-specific molecule and a DNA-binding domain, wherein said compound is a peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor- specific molecule at the time the invention was filed.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d

at 1405. The court also stated that a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

It is noted that as of the filing date a few compounds like the claimed compounds were known in the art (for example, Steffen et al. (Proc. Natl. Acad. Sci. USA July 8, 2003, 100: 8448-8453, IDS) and WO 01/73433 A2 (Minucci et al. October 4, 2001)), however, these few compounds fails to adequately describe an entire genus because the genus is highly variant encompassing members which differ significantly in structure from the art known compounds.

In the instant case the genus is only described as a definition by function (i.e. binding and delocalizing a tumor specific molecule), and beyond that of a few examples of such compounds in the art, one of skill in the art cannot readily visualize or recognize the identity of members of the genus in the absence of knowledge as to what that material consists of.

8. Claims 37-51, 58-60 and 77 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The limitation of a compound comprising a first binding domain for a tumor-specific molecule and a second binding domain to effect dyslocalization, wherein said compound is able to effect dyslocalization of the tumor-specific molecule claimed in 37-51 and 77 and the limitation of a medicament comprising a compound comprising a binding domain for a tumor-specific molecule and a DNA-binding domain, wherein said compound is a peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor- specific molecule claimed in claims 58-60 have no clear support in the specification and the claims as originally filed. Applicants pointed to support for the amended claim in the specification and original claims, in particular Figure 1C. A review of the specification and claims as originally filed discloses support for a compound/medicament that comprises the peptide sequence of the c-myb DNA binding domain and the peptide sequence of the AML-1 binding domain of the myeloid elf like factor/SEQ ID NO: 1, see original claim 1. The suggested support is not found persuasive because there is nothing in the specification to suggest the broadly claimed compound comprising a second binding domain to effect dyslocalization or the broadly claimed or compound comprising a binding domain for a tumor-specific molecule and a DNA-binding domain, wherein said compound is a peptide, oligoprotein, protein, or fusion protein and is able to effect dyslocalization of the tumor- specific molecule. Thus the subject matter claimed in claims 37-53, 58-60 and 77 broadens the scope of the invention as originally disclosed in the specification and claims originally filed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 37-53, 58-60 and 77 are rejected under 35 U.S.C. 102(a) as being anticipated by Steffen et al. (Proc. Natl. Acad. Sci. USA July 8, 2003, 100: 8448-8453, IDS).

It is noted that the recitation of "a medicament" in claim 58 is merely suggestive of an intended use that does not result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art and thus is not given weight for comparison of the claims with the prior art.

Additionally, one of skill in the art one immediately envision putting the GFP-M&M in a pharmaceutically acceptable carrier such as phosphate buffered saline for storage and administration to test samples. Furthermore, given that GFP-M&M alone or in a pharmaceutically acceptable carrier such as phosphate buffered saline could be administered orally, intravenously, or intramuscularly and such formulations are not limited by specification or the claims, claim 60 is anticipated.

Steffen et al. teach that AML1-ETO is a fusion protein in acute myeloid leukemia produced by the t(8;21) balanced translocation. Steffen et al. teach GFP-M&M that was constructed from the DNA binding domain of Myb and the AML-1 binding domain of myeloid Elf-1 like factor (MEF), see Abstract and Materials & Methods. Steffen et al. teach that this

protein associated with AML1-ETO and directed the complex to MYB-responsive promoters in vitro and in vivo. In the presence of AML1-ETO, the chimeric protein repressed the activity of MYB-responsive promoters, rapidly induced apoptosis, and specifically inhibited colony growth, see Abstract and figures.

Although the reference does not specifically state that the first binding domain has an affinity of 10^{-5} to 10^{-12} or a binding affinity of 10^{-7} to 10^{-9} or that GFP-M&M has the sequence shown in SEQ ID NO: 1, given that four of the eight authors of the paper are co-inventors of the instant application, the claimed product appears to be the same as the prior art product (GFP-M&M), absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977).

10. Claims 37, 41-45, and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by McWhirter et al. (Mol. and Cell. Biol. 1993, 13: 7587-759) as evidenced by Muller et al. (Mol. and Cell. Biol. 1992, 12:5087-5093).

It is noted that given the indefinite nature of claims 42 and 43, given their broadest reasonable interpretation, claims 42 and 43 are drawn to the first binding domain having any binding affinity to any other molecule.

McWhirter et al. teach that BCR-Abl is a tumor specific fusion protein of the BCR and Abl genes that is found in chronic myelogenous leukemia and acute lymphocytic leukemia, see

p. 7587, 2nd col. McWhirter et al. teach that the BCR sequences of BCR-Abl proteins alter the sub-cellular localization of the Abl protein by blocking its nuclear translocation and activating the F-actin binding functions, see p. 7587, 2nd col. and fig. 6. McWhirter et al. teach that the Bcr domain of BCR-Abl contains two binding domains that contribute to the oligomerization and altered localization of BCR-Abl. Domain 1 is a coiled-coiled domain that facilitates homo-tetramerization of BCR-Abl, see Abstract and Figure 6. Domain 2 binds the SH2 domain of Abl and activates Abl, see p. 7587, 2nd col. and fig. 6. Mueller et al. teach that the SH2 domain of Abl binds tyrosine phosphorylated c-Abl 1b with affinity of 5 $x10^{-7}$ M and binds BCR with an affinity of 10^{-5} M, see abstract and p. 5089-2nd col. Thus, BCR-Abl is protein that has first binding domain that binds to a tumor specific molecule, itself, and a second binding domain to effect dyslocalization of itself, the tumor specific molecule to the cytoplasm and F-actin.

11. Claims 37, 41-44, 47, 58-60 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/73433 A2 (Minucci et al. October 4, 2001) evidenced by Prokocimer et al. (Blood 1994 84:2391-2411).

It is noted that given the indefinite nature of claims 42 and 43, given their broadest reasonable interpretation, claims 42 and 43 are drawn to the first binding domain having any binding affinity to any other molecule.

WO 01/73433 teaches a fusion protein comprising the coiled coil (CC) region of the transcription factor PML-fused to the full length p53 tumor suppressor protein, see page 61. WO 01/73433 teaches that the p53-CC protein binds to p53 through the p53 tetramerization domain and PML CC domain and prevents p53 from entering the nucleus; see pages 61-63 and Fig. 11. Prokocimer et al. teach that p53 is tumor suppressor that is deleted in cancers and has a DNA

binding domain and a tetramerization domain for tetramerization, see Fig. 1 and page 2391. Thus the p53-CC protein is a protein comprising a binding domain for a tumor specific molecule, the tetramerization domain, a second binding domain to effect dyslocalization, the PML CC domain, and a DNA binding domain. WO 01/73433 teaches putting the compositions of the invention in pharmaceutically acceptable carriers, see p. 21. Given that in a pharmaceutically acceptable carrier could be administered orally, intravenously, or intramuscularly and such formulations are not limited by specification or the claims, claim 60 is anticipated.

12. No claims allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to PETER J. REDDIG whose telephone number is (571)272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Helms Larry can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/
Examiner, Art Unit 1642